

## PATENT COOPERATION TREATY

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NOTIFICATION OF ELECTION  
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark  
Office  
(Box PCT)  
Crystal Plaza 2  
Washington, DC 20231  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 25 July 1997 (25.07.97)	United States Patent and Trademark Office (Box PCT) Crystal Plaza 2 Washington, DC 20231 ETATS-UNIS D'AMERIQUE
International application No. PCT/GB97/00232	Applicant's or agent's file reference N72652 GCW
International filing date (day/month/year) 27 January 1997 (27.01.97)	Priority date (day/month/year) 25 January 1996 (25.01.96)
Applicant BROWN, Susanne, Moira et al	

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:

09 July 1997 (09.07.97)

 in a notice effecting later election filed with the International Bureau on:2. The election  was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Nicola Wolff Telephone No.: (41-22) 338.83.38
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Date of mailing: 31 July 1997 (31.07.97)	
International application No.: PCT/GB97/00232	Applicant's or agent's file reference: N72652 GCW
International filing date: 27 January 1997 (27.01.97)	Priority date: 25 January 1996 (25.01.96)
Applicant: BROWN, Susanne, Moira et al	

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## PATENT COOPERATION TREATY

09 APR 1998

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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference N.72652 GCW	<b>FOR FURTHER ACTION</b>		See Notification of Transmittal of International Preliminary Examination Report (PCT/IPEA/416)
International application No. PCT/GB97/00232	International filing date (day/month/year) 27/01/1997	Priority date (day/month/year) 25/01/1996	
International Patent Classification (IPC) or national classification and IPC A61K35/76			
Applicant MEDICAL RESEARCH COUNCIL et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I  Basis of the report
- II  Priority
- III  Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV  Lack of unity of invention
- V  Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI  Certain documents cited
- VII  Certain defects in the international application
- VIII  Certain observations on the international application

Date of submission of the demand 09/07/1997	Date of completion of this report 07.04.98
Name and mailing address of the IPEA/ European Patent Office D-80298 Munich Tel. (+49-89) 2399-0. Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer Taylor, G Telephone No. (+49-89) 2399-8406



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB97/00232

**I. Basis of the report**

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

**Description, pages:**

1-24 as originally filed

**Claims, No.:**

1-12 as originally filed

**Drawings, sheets:**

1/4-4/4 as originally filed

2. The amendments have resulted in the cancellation of:

the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

3.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB97/00232

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Yes:	Claims 7-10
	No:	Claims 1-6, 11 and 12
Inventive step (IS)	Yes:	Claims
	No:	Claims 1-12
Industrial applicability (IA)	Yes:	Claims 1-12 (But see Separate Sheet, Item 3)
	No:	Claims

**2. Citations and explanations**

**see separate sheet**

**VI. Certain documents cited**

**1. Certain published documents (Rule 70.10)**

and / or

**2. Non-written disclosures (Rule 70.9)**

**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

**see separate sheet**

INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB97/00232

1. Claims 1-6, 11 and 12 do not appear to meet the requirements of Art. 33(2) PCT.

1.1 Claims 1-6 and 11 do not appear to be novel over the following disclosures:

**WO 96/00007 (D1)**, which is relevant to claims 1-6 and 11, describes a method for killing tumour cells in a subject comprising the step of administering to said subject a pharmaceutical composition comprising a herpes simple virus vector, such as HSV-1, that is altered in the  $\gamma$ 34.5 gene. The tumour cells can be melanoma cells or mesothelioma cells (see claims; p.4, line 30 to p.6, line 15; p.23, line 10 to p.24, line 38).

**WO 93/19591 (D2)**, which is relevant to claims 1-4 and 11, describes the use of an HSV-1 virus which has been modified in the  $\gamma$ 34.5 gene (see: p.12, lines 3-15; claims, especially 1 and 2) for the treatment of tumorigenic diseases "both in the CNS and in all other parts of the body" (p.10, lines 29-32).

It is also noted that the term 'vector' is a general one which encompasses the mutant virus itself, as can be seen from e.g. Example 1 of D1, and D2, p.12, lines 3-5.

1.2 Claim 12 does not appear to be acceptable because pharmaceutical agents containing a mutant herpes simplex virus which has been modified in the  $\gamma$ 34.5 gene such that the gene is non-functional are already known from the above and following documents. Therefore, only claims directed to a second (further) medical use are acceptable.

**Virology 1995, 211, 94 (D3)** discloses an injection solution of HSV 1716 for the treatment of neuronal tumours in mice (see: abstract; p.95, col.2, last para.; p.98, col.2, 'Discussion').

**WO 92/13943 (D4)** describes a vaccine comprising HSV-1 1716 (claims 16 & 8).

**WO 92/04050 (D5)** discloses a pharmaceutical comprising an HSV-1 virus which has been modified in the  $\gamma$ 34.5 gene (p.3, line 11 to p.5, line 19).

**Medline Abstract 96083561 (D6)** discloses the use of an HSV-1 virus which has been modified in the  $\gamma$ 34.5 gene in a composition for the treatment of mice having the NT2 tumour.

2. Novel features of claims 1-6, and claims 7-10, do not appear to meet the requirements of Art. 33(3) PCT.

The closest prior art document would appear to be **D1**, which describes a method for killing

INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/GB97/00232

tumour cells in a subject comprising the step of administering to said subject a pharmaceutical composition comprising a herpes simple virus vector, such as HSV-1, that is altered in the  $\gamma$ 34.5 gene. The tumour cells can be melanoma cells or mesothelioma cells (see claims; p.4, line 30 to p.6, line 15; p.23, line 10 to p.24, line 38).

- 2.1 The difference between the teachings of **D1** and the novel subject-matter of claims 1-6 would appear to reside in the treatment of ovarian carcinoma or bladder cancer. However, given the disclosure of **D2** that an HSV-1 virus which has been modified in the  $\gamma$ 34.5 gene can be used for the treatment of tumorigenic diseases "both in the CNS and in all other parts of the body" (p.10, lines 29-32), the skilled man would be led to investigate the treatment of other tumours such as ovarian or bladder. The combination of the teachings of **D1** and **D2** would thus appear to render obvious the novel subject-matter of claims 1-6.
- 2.2 The difference between the teachings of **D1** and the subject-matter of claims 7-10 would appear to reside in the use of specific strains of HSV-1, ultimately in the use of HSV-1 1716. However, **D3** discloses the use of HSV-1 1716 for the treatment of neuronal tumours in mice (see: abstract; p.95, col.2, last para.; p.98, col.2, 'Discussion') and in vitro experiments showing the efficacy of HSV-1 1716 against melanoma, that is against a non-neuronal cancer (see: pp.96-98, 'Results'; pp.98- 100, 'Discussion'). The combination of the teachings of these two documents, i.e. to use the strains according to **D3** in the method of **D1** would have been obvious in view of the in vitro experiments described in **D3**. Thus, the subject-matter of claims 7-10 would appear obvious.
3. For the assessment of the present claim 11 on the question whether it is industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
4. The following documents are cited under Rules 64.3 and 70.10 PCT:

**WO 96/03997**

Published on: 15.02.96  
Filing date: 28.07.95  
Priority: 29.07.94

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB97/00232

**WO 96/39841**

Published on: 19.12.96

Filing date: 06.06.96

Priority: 07.06.95

**Proc. Am. Assoc. Cancer Res. 1996, 37 (March), 342, Abstract 2335.**

Published on: March 1996

Disclosure: 24.04.96

5. There is apparently no description of a medicament or disclosure of any pharmacological data in the application documents which pertain to the use of such compositions as medicaments. The applicant should therefore be aware that objections could be raised during substantive examination in the National Phase that a solution to (at least part of) the technical problem has not been provided.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>N72652 GCW</b>	<b>FOR FURTHER ACTION</b>	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. <b>PCT/GB 97/00232</b>	International filing date ( <i>day/month/year</i> ) <b>27/01/1997</b>	(Earliest) Priority Date ( <i>day/month/year</i> ) <b>25/01/1996</b>
Applicant <b>MEDICAL RESEARCH COUNCIL et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1.  Certain claims were found unsearchable (see Box I).
2.  Unity of invention is lacking (see Box II).
3.  The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
  - filed with the international application.
  - furnished by the applicant separately from the international application,
    - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
    - Transcribed by this Authority
4. With regard to the title,
  - the text is approved as submitted by the applicant.
  - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
  - the text is approved as submitted by the applicant.
  - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:
  - Figure No. \_\_\_\_\_  as suggested by the applicant.
  - because the applicant failed to suggest a figure.
  - because this figure better characterizes the invention.

None of the figures.

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/GB 97/00232

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 11 because they relate to subject matter not required to be searched by this Authority, namely:  
**Remark:** Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/00232

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K35/76

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VIROLOGY, vol. 211, no. 1, 1 August 1995, pages 94-101, XP000561228 RANDAZZO B P ET AL: "TREATMENT OF EXPERIMENTAL INTRACRANIAL MURINE MELANOMA WITH A NEUROATTENUATED HERPES SIMPLEX VIRUS 1 MUTANT" see page 94, abstract</p> <p>---</p> <p>WO 96 00007 A (UNIV GEORGETOWN) 4 January 1996 see page 4, line 30 - page 6, line 15 see page 23 - page 28; example 1</p> <p>---</p> <p>---</p>	1-12
X		1-6,11, 12

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

1

Date of the actual completion of the international search

17 April 1997

Date of mailing of the international search report

25.04.97

## Name and mailing address of the ISA

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Authorized officer

Sitch, W

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/00232

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 13943/A (SMITHKLINE BEECHAM BIOLOG) 20 August 1992 cited in the application see page 2, line 19 - page 4, line 31 see page 5, line 14 - page 9, line 16 ---	12
X	WO 92 04050/A (ROIZMAN BERNARD) 19 March 1992 see page 3, line 11 - page 5, line 19 ---	12
X	WO 93 19591/A (ARCH DEV CORP) 14 October 1993 see page 10, line 29 - page 11, line 9 ---	12
X	DATABASE MEDLINE FILE SERVER STN KARLSRUHE ABSTRACT 96083561, KESARI ET AL: "THERAPY OF EXPERIMENTAL HUMAN BRAIN TUMOURS USING A NEUROATTENUATED HERPES SIMPLEX VIRUS MUTANT" XP002029649 see abstract & LABORATORY INVESTIGATION, vol. 73, no. 5, November 1995, pages 636-648, ---	12
P,X	WO 96 03997/A (MEDICAL RES COUNCIL ;WISTAR INST (US); MACLEAN ALASDAIR RODERICK) 15 February 1996 cited in the application see page 4, paragraph 5 - page 8, paragraph 2 see page 18 - page 19; example 1 ---	1-12
P,X	WO 96 39841/A (UNIV GEORGETOWN) 19 December 1996 see page 7, line 15 - page 10, line 37 ---	1-6,11, 12
P,X	PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 37, March 1996, page 342 XP002029648 KUCHARCZUK ET AL: "REPLICATION-RESTRICTED HERPES SIMPLEX VIRUS-BASED TREATMENT OF LOCALIZED NON-CNS MALIGNANCY" see abstract 2335 -----	1-12

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/00232

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9600007 A	04-01-96	US 5585096 A AU 2906095 A EP 0766512 A	17-12-96 19-01-96 09-04-97
WO 9213943 A	20-08-92	AU 657731 B AU 1182992 A CA 2101639 A EP 0571410 A JP 6507066 T NZ 241476 A NZ 245842 A	23-03-95 07-09-92 01-08-92 01-12-93 11-08-94 23-12-93 23-12-93
WO 9204050 A	19-03-92	US 5328688 A AU 658838 B AU 8741891 A CA 2072627 A EP 0500917 A JP 5503017 T	12-07-94 04-05-95 30-03-92 11-03-92 02-09-92 27-05-93
WO 9319591 A	14-10-93	AU 3781893 A EP 0675961 A JP 7507997 T	08-11-93 11-10-95 07-09-95
WO 9603997 A	15-02-96	AU 3119995 A CA 2196315 A	04-03-96 15-02-96
WO 9639841 A	19-12-96	AU 6149596 A	30-12-96